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The Analysis Study of Relationship of Peripheral Perfusion, Micro Circulation and Mortality in Sepsis : A Comprehensive Systematic Review

[1]Fajar Nurochman Sidik, [2]Raka Jati Prasetya, [3]Army Zaka Anwary

[1]General Practitioner, Jampang Kulon Regional General Hospital, Sukabumi Regency, West Java, Indonesia

[2]Fellowship Intensive Care, Departement of Anesthesiology and Intensive Care, Faculty of Medicine Padjadjaran University, dr. Hasan Sadikin National Refferal and Teaching Hospital, Bandung City, West Java, Indonesia

[3]Anesthesiology and Intensive Care Consultant, Departement of Anesthesiology and Intensive Care, Faculty of Medicine Bandung Islamic University, Al Ihsan Regional General Hospital, Bandung Regency, West Java, Indonesia

Correspondence : fajar.nurch@gmail.com

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ABSTRACT

Background: Sepsis, a leading cause of death worldwide, is characterized by abnormal body response to infections, leading to organ malfunction. Monitoring peripheral perfusion is crucial for identifying sepsis, evaluating treatment effectiveness, and predicting outcomes. Noninvasive metrics like capillary refill time and peripheral perfusion index can predict outcomes and target resuscitation in septic patients. Understanding the correlation between peripheral perfusion and microcirculation in sepsis could alleviate its impact.

Methods: Adhering to the PRISMA 2020 principles, this systematic review focused on analyzing complete English literature texts published from 2014 to 2024. Editorials and review articles published in the same journal as the submission were only accepted if they had a DOI (Digital Object Identifier). Several websites, such as ScienceDirect, PubMed, and SagePub, were used to collect the literature.

Result: The study examined over 200 publications sourced from recognized platforms such as Science Direct, SagePub, and PubMed. Following the determination that eight publications required more scrutiny, a comprehensive examination of the full body of literature was conducted.

Conclusion: Peripheral perfusion and microcirculation are crucial factors in patient well-being and mortality in septic patients. Using orthogonal polarization spectrum technology and real-time monitoring of microcirculation images can aid in identifying and initiating resuscitation, which is linked to a decrease in multiorgan failure and SOFA score. Newer technologies like the objective CRI device offer promising tools for monitoring shock status at the bedside.

Keyword:sepsis, peripheral perfusion,microcirculation, mortality

INTRODUCTION

Sepsis is characterized by an abnormal response of the body to an infection, resulting in the malfunctioning of organs.[1] Despite advancements in clinical outcomes, sepsis continues to make up a considerable number of critically ill patients and remains one of the leading causes of death worldwide.[2,3] International standards stress the importance of promptly identifying, evaluating, and treating septic shock by early delivery of antibiotics, hydration therapy, and vasopressor infusion. One potential reason could be the ongoing inadequate blood flow to the tissues, even when the overall circulation has been restored to normal levels.[4]

Tissue perfusion monitoring has emerged as a vital method for detecting sepsis, assessing the efficacy of its therapy, and forecasting the prognosis.[5,6]Clinicians can evaluate the peripheral perfusion of cutaneous microvessels by employing noninvasive bedside metrics such as the capillary refill time (CRT) and the peripheral perfusion index (PI). These metrics are simply measured on the skin, which is readily accessible.[7]The rationale for monitoring peripheral perfusion is based on the recognition that peripheral tissues, such as the skin and muscles, are the first to be affected by reduced blood flow during sepsis and the last to recover blood flow after resuscitation..[8]Abundant research has shown that noninvasive peripheral perfusion can accurately forecast results,9 and can be regarded as a reasonable objective for resuscitation in septic patients lacking precise criteria.[5]

The typical hemodynamic goals for resuscitating patients with septic shock involve the utilization of macro-hemodynamic indices, such as heart rate, mean arterial pressure, and central venous pressure. Nevertheless, sustained changes in the blood flow of small blood vessels, even after the larger-scale circulation has been restored, can fail organs. De Backer et al. conducted a meta-analysis involving 252 patients and found that changes in microcirculatory perfusion can be used to predict death in severe infections. However, mean arterial pressure or cardiac output was not found to be predictive of mortality.[10] Administering higher dosages of dobutamine to enhance cardiac output did not result in improved blood flow in the sublingual region of critically sick patients, as observed in a study by Hernandez in 2013.[11] According to another study conducted by Thooft in 2011, changing the norepinephrine dose to control mean arterial pressure had inconsistent and unpredictable impacts on the flow of blood in the small blood vessels, sometimes leading to deterioration.[12] Ince has termed the dissociation between macro- and microcirculatory compartments as a "loss of hemodynamic coherence."[13]

This highlights the importance of evaluating tissue perfusion in end organs and developing methods to monitor microcirculatory blood flow in patients with septic shock.[4,13] Gaining insight into the correlation between peripheral perfusion and microcirculation in sepsis might alleviate the impact of this illness. This systematic literature review intended to investigate the correlation between peripheral perfusion and microcirculation in sepsis mortality, using research conducted within the last ten years.

METHODS

Protocol

The study's author adhered closely to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria to guarantee full compliance with all requirements. A meticulous methodology was employed to provide precise and compelling research results.

Criteria for Eligibility

This article offers a comprehensive review of studies carried out in the last decade on the correlation between peripheral perfusion, microcirculation, and mortality in sepsis. This program aims to elucidate and optimize patient care methods through thorough data analysis. The main aim of this thesis is to highlight important themes that are found in a range of literary works.

In order to guarantee the precision of the data utilized in this research, stringent criteria for inclusion and exclusion were enforced. Any material that has been officially released in the English language from 2014 to 2024 is considered eligible for inclusion. The exclusion criteria encompass published reviews, editorials, submissions lacking a DOI, and duplicate entries within the same journal.

Search Strategy

The study's keywords include "peripheral perfusion, micro circulation, sepsis, mortality, outcomes, death". For this research, the following Boolean MeSH keywords were entered into the databases: (((“peripheral perfusion”[MeSH Terms] OR “peripheral perfusion“[All Fields] AND “sepsis”[All Fields]) OR (“micro circulation”[MeSH Terms] OR“micro circulation”[All Fields] AND “sepsis”[All Fields]) AND (“sepsis”[MeSH Terms] OR “peripheral perfusion”[All Fields] OR “circulation”[All Fields] OR “mortality”[MeSH Subheading] OR “outcomes”[All Fields] OR “death”[All Fields]))).

Data retrieval

Prior to commencing this comprehensive analysis, the authors meticulously assessed the relevance of each publication by scrutinizing its title and abstract. Only research that fulfilled the aims and met the inclusion criteria of the article were given greater significance. A distinct and uniform pattern became evident after conducting repeated searches. Only contributions written in English were permitted. The screening process was quite thorough and resulted in information that was directly relevant to the topic of the study and met all the established criteria for inclusion. Research that did not meet these criteria was typically ignored and its results were not considered significant. The examination encompassed a diverse array of data, comprising factors, titles, authors, publication dates, places, and study methodologies.

Quality Assessment and Data Synthesis

The authors themselves meticulously review the abstract and title of each article to identify those that necessitate additional examination. Subsequently, every document that was originally under consideration had to undergo a meticulous examination. The evaluation findings influenced the choice of the review papers. This criterion facilitated the expedited selection of publications for further study, so enabling a more comprehensive assessment of previous research and the context in which it was evaluated.

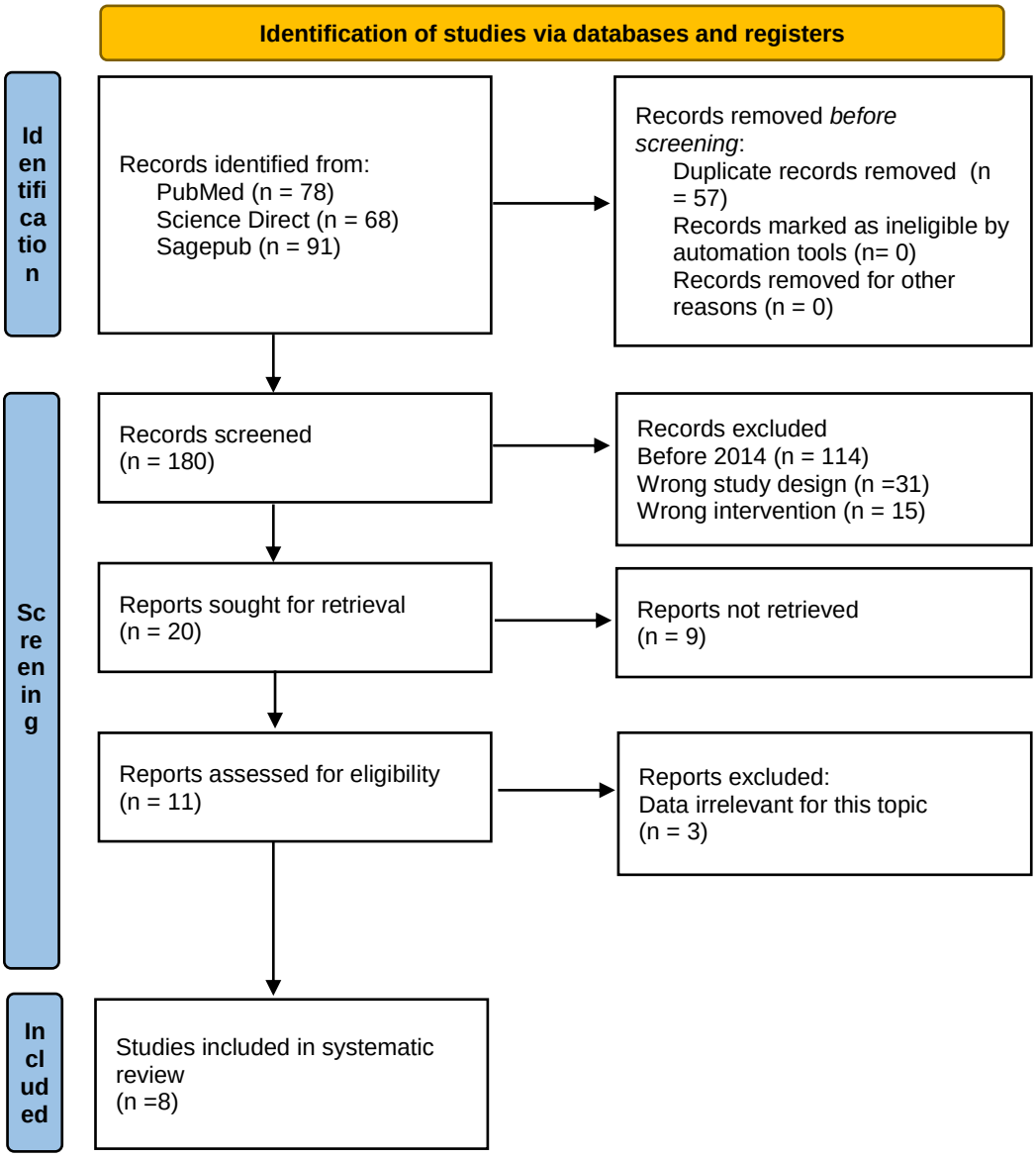

Figure 1. Article search flow chart

RESULT

To initiate the inquiry, our team diligently gathered a significant assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected eight papers that were considered highly relevant to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our inquiry, we have furnished a concise summary of the evaluated information in Table 1.

Table 1. The literature included in this study

r		d	e	
al.[14] (2018)		vational study	ients	tudy analyzed systemic lynamics and irculation data in patients a first 6 hour lactate

				nce (LC) of ≥20%. s showed lower PI and at T6 in patients with LC compared to those with 20%. Participants were d into high PI and high groups, with the lowest in the low PI and low group. Post hoc tests d significant differences day survival rates.
i et al.[4]		ive Review		, a leading cause of ve care unit admission, to high morbidity and ity. Perfusion of eral blood flow is crucial suscitation, as persistent ions can lead to organ . Noninvasive bedside eters like skin ratures, capillary refill and mottling can quickly te peripheral tissue ion, reducing the need for onal markers.
ne et 019)		vational study	ients	udy discovered a notable ation between circulatory oxygen ion and PAI-1 levels in duals who had a mottling of 2, as opposed to those a score of 0. Higher ng score and lower circulatory oxygen ion were indicative of a likelihood of dying 28 days. However, the on of endothelium rkers did not enhance the to predict death based on icrocirculatory perfusion s.
Miranda et 2020)		vational t	tients	ial included a total of 113 ts, all of whom were ed to the SA-AKI group. esults indicated that the KI group had greater rates eripheral hypoperfusion.

				ver, after making ments for several les, this difference lost its cal significance. ion anomalies observed in oup of patients with SA- were shown to be ated with increased ity rates at 28 days, ting a strong predictive for death within the first urs.
co et al.[17]		w		eral perfusion measures hemodynamic status in lly ill patients, enabling therapy and reducing associated death. New logies, such as reflected ransmitted light, aim to ve accuracy and tous hemodynamic oring across clinical gs.
eans et al.[18]		w		lity in septic shock ranges 20% to 100%, with ory shock leading to early atory failure. circulation plays a crucial reducing mortality, and lizing sympathetic ctivity can improve circulation by recouping ries and systemic ation.
Miranda et 2023)		t study	tients	study analyzed 226 ts, with 117 in the low group and 109 in the high group. The first day ity was higher in the high group, maintaining ostic significance after ariate adjustment. The ral ΔPPI peak values d no maintenance over rst 48 hours in either
ne et al.[20]		vational study	ients	study did not find any cant correlation between

				distribution of skin rature in the front part of high and knee and the ce of mottling or survival 8 days. This suggests that d thermography has the ial to be used in ting the patterns of skin rature in patients with shock who have been itated.

Pan et al.'s 2018 study found no significant differences in systemic hemodynamic parameters such as CVP, SvO, MAP, and flow in septic shock patients. However, the PI of the LC <20% group was significantly lower than the LC ≥20% group at the time of treatment. The study also found that the ΔPPV in the LC <20% group was lower than the LC ≥20% group. The study also found significant differences in 28-day survival rates among the four groups.[14]

Hariri's research on septic shock highlights the importance of peripheral evaluation in understanding the pathophysiology of the condition. Perfusion, influenced by skin temperature, capillary refill time, and color, can be observed through subjective assessment. The study suggests that patients with cold hands, abnormal skin color, and lower central venous saturation have a worse prognosis. The peripheral perfusion index (PPI) is an early predictor of central hypovolemia.[4]

Kazune's study revealed that skin μHbSO2 levels were higher in patients who survived septic shock than those who died, with higher μHbSO2 and lower SOFA score values predicting 28-day mortality. However, there was no association between endothelial activation biomarkers and 28-day survival.[15]

The research conducted by de Miranda et al. included 141 individuals with sepsis who underwent evaluation of peripheral perfusion following fluid resuscitation. The SA-AKI group exhibited elevated APACHE and SOFA scores, reduced urine production, and increased arterial lactate levels. The SA-AKI group had a 55% greater 28-day in-hospital mortality rate compared to the non-SA-AKI group. Higher rates of 28-day in-hospital mortality were observed in the SA-AKI group due to abnormalities in peripheral perfusion.[16]

Falotico et al.'s study highlights the development of technology to objectively calculate CRT, eliminating variability in manual measurements. Digitally measured CRT (DCRT) was introduced for assessing dehydration in children with gastroenteritis. Kawaguchi et al. improved hemodynamic monitoring precision with fingernail compression. John et al. used video mode polarization spectroscopy, but its design is limited in clinical settings.[17]

Petitjeans' study highlights the importance of addressing microcirculation and immunoparalysis in septic shock patients, suggesting that prolonged sympathetic hyperactivity can be detrimental and normalized sympathetic activity can be beneficial.[18]

de Miranda et al. highlighted the advantages of peripheral ischemic microvascular reserve (PIMR) assessment using the PPI/PORH combination, including fast, low-cost, and good predictive quality for survival, making it a potential prognostic enrichment tool for clinical routine.[19]

Kazune's research linked septic shock to decreased skin temperature, but did not find a correlation between changes in skin temperature distribution and resuscitated patients. This suggests that greater mottling scores are indicative of septic shock.[20]

DISCUSSION

Microcirculation, a crucial factor in patient well-being, strongly correlates with mortality in septic patients. The peripheral perfusion index (PI) and sublingual microcirculation measures are often used to assess the ratio of pulsatile blood flow to nonfluctuating blood flow. However, there is insufficient data to support the notion that alterations in PI can accurately indicate the perfusion and oxygenation of central tissues. Utilizing orthogonal polarization spectrum (OPS) technology and continuously monitoring microcirculation images in real time can aid in identifying and initiating microcirculation resuscitation.[14] Microcirculation, peripheral perfusion index (PI), and tissue perfusion are essential parameters for predicting death in adult patients who are severely ill. Decreased PI and ΔPPV indicate elevated SOFA scores and a negative prognosis for mortality within 28 days. Combining these two indications can enhance the ability to accurately predict prognosis. Resuscitating the microcirculation is equally crucial as resuscitating the macrocirculation, and initiating early resuscitation of the microcirculation is linked to a decrease in multiorgan failure and SOFA score.[21]

Peripheral perfusion is a valuable tool in managing sepsis, particularly in patients with mild arterial hypotension. Studies have shown that global hemodynamic improvement within the first hours following resuscitation, based on blood volume optimization and catecholamine use, is associated with improved mottling. Finger-tip CRT is quickly normalized in septic shock patients within 2-6 hours after resuscitation, while hyperlactatemia requires a longer recovery time.[22]The significance of microcirculatory disturbances in the evolution of sepsis-related organic dysfunctions is underscored by the fact that patients with sepsis-associated acute kidney injury (SA-AKI) have a death rate that is two times higher than non-SA-AKI patients.[10]Continued inadequate blood flow to the peripheral tissues, even after correcting overall blood circulation, is an early and separate indicator of mortality in patients with sepsis.[23]Additional research is needed to validate this hypothesis and establish the cause-and-effect connection between peripheral hypoperfusion and mortality in individuals with sepsis.[16]

Peripheral perfusion measures are crucial for assessing the hemodynamic status of critically ill patients, and newer technologies like the objective CRI device offer promising tools for monitoring shock status at the bedside.[17] it is a crucial factor in managing septic shock, as it can help reduce inflammation, systemic vasodilation, emergence of delirium, delayed emergence from conventional sedation, duration of controlled mechanical ventilation, CCU stay, and mortality.[18] However, prolonged sympathetic hyperactivity can have detrimental effects and a benefit of normalized sympathetic activity.[24] A study reveals a relationship between peripheral ischemic resistance (PIMR) and mortality in sepsis, primarily in the septic shock subgroup. This prognostic enrichment is valid up to 24 hours after resuscitation and can be easily obtained at the bedside.[19] Patients with a more significant vasodilatation response after limb ischemia exhibited higher mortality.[25] The high PIMR group showed two times higher mortality than the low PIMR group in the septic shock subgroup.[19]

This study examines the temperature distribution pattern in the skin of the knee and upper thigh in individuals who have been resuscitated from septic shock, using infrared thermography. There is no notable variation in the distribution of skin temperature across

patients with different mottling scores. However, if mottling is present, non-survivors tend to have lower skin temperatures.[20]Greater variations in skin temperature and a larger temperature difference between a measurement location closer to the body and a site farther away are considered to provide more precise indications of aberrant blood flow in the extremities compared to absolute skin temperature measurements.[26,27]

The mottling score is linked to a decrease in the warmth of the skin in the knee area, which may be caused by irregularities in blood flow in the region supplied by the genicular arteries. The reduced blood flow in this region can be attributed to an elevation in systemic vascular resistance and a decline in cardiac output. Active dynamic thermography (ADT) has the capacity to bring about substantial enhancements.[28,29]Nevertheless, the question that has not been answered yet is whether the occurrence of mottling and alterations in skin temperature in the knee region and anterior thigh are caused by the same disturbance in microcirculatory perfusion, or if they are separate indicators of peripheral perfusion. To gain a more comprehensive understanding of the therapeutic consequences of these devices and their potential applications in managing septic shock, it is necessary to conduct a study with a larger group of patients.[20]

CONCLUSION

Peripheral perfusion, a crucial factor in patient well-being, strongly correlates with mortality in septic patients. The peripheral perfusion index (PI) and sublingual microcirculation measures are often used to assess the ratio of pulsatile blood flow to nonfluctuating blood flow. However, there is insufficient data to support the notion that alterations in PI can accurately indicate the perfusion and oxygenation of central tissues. Utilizing orthogonal polarization spectrum (OPS) technology and continuously monitoring microcirculation images in real time can aid in identifying and initiating microcirculation resuscitation. Resuscitating the microcirculation is equally crucial as resuscitating the macrocirculation, and initiating early resuscitation is linked to a decrease in multiorgan failure and SOFA score. Persistent peripheral hypoperfusion, despite correction of systemic hemodynamics, is an early and independent predictive marker for mortality in sepsis patients. Newer technologies like the objective CRI device offer promising tools for monitoring shock status at the bedside.

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